CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-903

MEDICAL REVIEW(S)

NDA 20-903

AUG 6 1998

CLINICAL REVIEW

Date submitted: December 3, 1997
Date received: December 5, 1997
Date assigned: December 8, 1997
Date completed: June 30, 1998

1. General Information

Sponsor: Schering Corporation
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

Drug:
Generic: ribavirin
Trade: Rebetol™
Chemical: 1-β-D-Ribofuranosyl-1-H-1,2,4-triazole-3-carboximide

Route: Oral

Dosage Form: Capsule

Strength: 200 mg

Proposed Indication: Treatment of chronic HCV infection in patients with compensated liver disease who have relapsed following previous interferon therapy

Related INDs: [redacted]

Related NDAs: [redacted]

Related PLAs: Intron® A (interferon alfa-2b-recombinant)

Related Documents:
Medical Officer review of protocols C95-144 and I95-145 dated: March 5, 1996
End-of-phase two letter dated: March 7, 1996
Minutes of Pre-NDA meeting dated: June 30, 1997
Responses to requests for information dated: December 18, 1997, January 12, 1998, January 13, 1998, January 15, 1998, January 16, 1998, January 20, 1998, March 6, 1998, March 20, 1998, March 26, 1998, April 17, 1998
4-Month Safety Update dated: March 26, 1998
Memorandum from DSI dated: May 4, 1998

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2. Summary

The applicant has submitted results from two double-blind, randomized trials (C95-144 and I95-145) of INTRON® A (Interferon alfa-2b-recombinant) with REBETOL™ (ribavirin) Capsules or placebo in patients with chronic hepatitis C virus (HCV) infection. To be eligible for inclusion into these trials, patients must have relapsed, defined as having elevated ALT levels, following a response to a previous course of alfa-interferon. A total of 345 male and female adult patients with compensated liver disease were randomized to receive treatment with INTRON A 3 MIU three times per week with either ribavirin 600 mg twice daily (INTRON A + ribavirin) or placebo (INTRON A + placebo) for 24 weeks followed by 24 weeks of off-therapy follow-up. The primary efficacy endpoints were based on virologic response and improvement in liver histology.

Sustained virologic response was defined as HCV-RNA below the limit of quantification of the assay by the end of therapy that was maintained throughout the follow-up period. Sustained virologic response was achieved by 43% and 48% of patients in the INTRON A + ribavirin combination arms of the two studies compared to a 3.9% and 5.2% in the two INTRON A − placebo-treated groups. In both studies, all of patients in the INTRON A + ribavirin treatment groups who were sustained virologic responders had achieved their initial virologic response by week 12 of therapy.

Histologic improvement, defined as ≥2 point improvement in components I+II−III of the Knodell HAI score were 49% and 51% in the two INTRON A + ribavirin groups of study and 42% compared to 36% and 31% for the two placebo groups, respectively. Although fibrosis (component IV) is an important marker of disease activity, inclusion of this parameter in the analyses did not appreciably affect histologic response rates. These data further support the conclusion that fibrosis did not worsen in study subjects.

Patients who achieved both a sustained virologic response and histologic improvement were considered overall responders. The results of study C95-144 demonstrated that a significantly higher proportion of patients treated with INTRON A + ribavirin had an overall response compared to patients treated with INTRON A − placebo: 30% versus 3%, respectively. The results of study I95-145 were similar: 35.4% of those treated with the combination were overall responders compared to 4.2% of INTRON A + placebo-treated patients.

Early ALT response (by week 12) was correlated with sustained virologic response in both studies. Also, a normal ALT value at week 48 was correlated with a HCV-RNA below the LOQ at week 48. Normalization of ALT was not highly correlated with histologic response and generally underestimated the histologic response to therapy.

Lower baseline HCV-RNA levels (≤2 million copies/mL) and non-Genotype 1 virus were weakly correlated with a favorable response to therapy. However, neither baseline ALT levels, HCV-RNA levels, or Knodell HAI score were predictive of a response to therapy.

Safety evaluations of over 25,000 patients who received INTRON A + ribavirin between August 1995 and the present were included in the safety data base. There have been 23 deaths reported in this database.

Approximately 98% of patients in the two clinical trials experienced adverse events. The occurrence of serious psychiatric (depression and suicidal behavior), hematological (anemia) and cardiovascular (myocardial infarction) events, some of which were associated with death, indicate that patients should be closely monitored during treatment. Patients with significant pre-existing cardiovascular, pulmonary, or psychiatric disease were excluded from these trials. Therefore, consideration to exclude patients with significant pre-existing cardiovascular or psychiatric disorders from receiving this combination therapy should be given.

Both agents are known to adversely affect pregnancy outcomes. Female patients and female partners of male patients who are receiving treatment who become pregnant will be at a significant risk for adverse birth outcomes. Evaluation of the incidence and outcomes of pregnancies will be important as these agents enter general clinical use.

In conclusion, based on the data submitted in NDA 20-903, the combination of INTRON A + ribavirin was more effective than re-treatment with INTRON A alone for the treatment of chronic HCV infection in patients with compensated liver disease who have relapsed following previous INTRON A monotherapy.

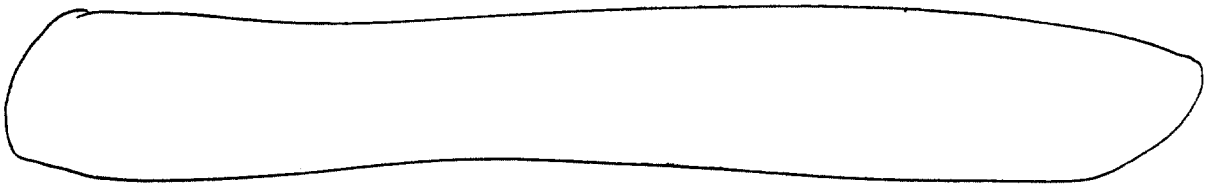
Adverse events occurred in nearly all of the patients in the two relapse studies. The types of events were consistent with those associated with either interferon or ribavirin therapy, although the frequency of events was generally higher in the combination arms of the two studies. The adverse events of primary concern were depression and anemia.

3. Background

3.1 Regulatory History

Ribavirin is a guanosine analogue that has *in vitro* antiviral activity against a number of different RNA viruses. The mechanism of action is unknown but several mechanisms have been suggested including depletion of intracellular triphosphate pools, inhibition of viral polymerase, inhibition of 5' capping, and inhibition of TH2 cytokines. Ribavirin enters the red blood cell and has an intracellular half-life of approximately 300 days.

Aerosolized ribavirin was approved in 1988, for the treatment of respiratory syncytial virus in infants. Anemia was the most common adverse event reported in clinical trials of ribavirin. Ribavirin has also been demonstrated to be mutagenic, teratogenic and embryocidal in animal studies. Aerosolized ribavirin is currently labeled as Pregnancy Category X.



Phase III protocols of ribavirin in combination with INTRON A were developed by [redacted] but were never initiated. In August 1995, oral ribavirin was licensed to Schering Corporation for further development for treating HCV infection. The rationale for development of ribavirin in combination with INTRON A was based on findings from a number of small pilot studies suggesting that a six month course of combination therapy was associated with sustained antiviral responses, as measured by reductions in HCV-RNA, ranging from 35-45% in patients naïve to interferon, and 30-40% in patients who had relapsed following previous interferon therapy.[1,2,3] These studies did not provide data on histologic responses.

The IND for the combination of Intron A/oral ribavirin was filed in January 1996. The protocol for study C95-144 was submitted with the IND; comments were provided March 5, 1996. In addition to comments on the proposed protocol, a request for information about lower doses of ribavirin was forwarded to the applicant. A pre-NDA meeting was held on June 30, 1997, and the NDA was submitted December 4, 1997.

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[1]Brillanti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa resistant chronic hepatitis C. Gastroenterology 1994; 107:812-6.

[2]Chemello L, Cavaletto L, Bernardinello E, et al. Response to ribavirin, to interferon and to a combination of both in patients with chronic hepatitis C and its relation to HCV genotypes. Symposium on hepatitis C virus and related viruses. San Diego, CA; 1994:204 (abstract).

[3]Lai MY, Kao JH, Yang PM, et al. Combination therapy of interferon and ribavirin in patients with chronic hepatitis C. Symposium on hepatitis C virus and related viruses. San Diego, CA; 1994:197 (abstract).

3.2 Natural History and Treatment of Hepatitis C

Hepatitis C is a viral infection that accounts for 20% of cases of acute viral hepatitis and 70% to 90% cases of chronic viral hepatitis. The hepatitis C virus is a single-stranded, positive-sense RNA virus in the Flaviviridae family. At least six distinct genotypes and 30 subtypes have been identified.

It is estimated that 3.5-4 million persons in the United States are chronically infected with HCV. Approximately 150,000-200,000 acute new infections occur each year, about 25-30% of which are diagnosed. Hepatitis C infection accounts for approximately 12,000 deaths annually and is now the leading cause of liver transplantation in the US.

HCV is transmitted primarily by the parenteral route. The risk of infusion-related hepatitis is in the range of 1 in 100,000 units transfused.

Infection with HCV is persistent. After initial exposure, HCV-RNA can usually be detected in the serum within 1-3 weeks. Within about 50 days almost all patients will develop liver cell injury, as shown by elevation of serum alanine transferase (ALT). The majority of patients are asymptomatic and anicteric. Twenty-five to 35% of patients develop symptoms such as fatigue, malaise, weakness, nausea, or anorexia, and become icteric. Fulminant liver failure is rare. Antibodies to HCV become detectable during the course of the illness; anti-HCV is detectable in 50-70% at the onset of symptoms and in 90% three months after onset of infection. HCV is self-limiting in 15% of cases with recovery characterized by disappearance of HCV-RNA and return of liver enzymes to normal. HCV genotypes 2 and 3, low serum HCV-RNA levels ($<1 \times 10^6$ copies/mL), and the absence of cirrhosis have been reported to be associated with more favorable responses to treatment with interferon monotherapy.[4]

HCV infection is not easily cleared by the host's immunologic defenses. Thus, nearly 85% of patients fail to clear the virus by 6 months and develop chronic hepatitis with persistent viremia. The majority will have abnormalities in ALT levels that can fluctuate widely. Antibodies to HCV or circulating viral RNA is present in virtually all patients. Chronic hepatitis C is generally insidious, generally progressing at a slow rate without signs or symptoms in the majority of patients during the first two decades after infection. Chronic hepatitis C infection leads to cirrhosis in about 20% of patients within two decades. Once cirrhosis is established, liver failure and portal hypertension can occur. Patients usually become jaundiced, and have ascities, variceal hemorrhage and encephalopathy. The rate of progression is highly variable. The relationship between ALT and disease severity, as judged by histology, is inconsistent.

Chronic hepatitis C infection is associated with increased risk of hepatocellular carcinoma (HCC). Most cases of HCV-related HCC occur in the presence of cirrhosis. HCC occurs more commonly in men than in women and in older than younger patients.

INTRON A® was approved for the treatment of chronic non-A, non-B hepatitis in February 1991. Intron A at a dose of 3 MIU TIW for six months produced end-of-treatment responses (normalization of serum ALT and loss of detectable HCV-RNA) of 40-50%, and sustained responses of 15-20% in interferon naïve patients. Increasing duration of treatment to 12 months has generally not been associated with higher end-of-treatment biochemical or virologic responses, but has had a marginal effect on increasing the sustained responses to 20-30%.[4]

In 1997, the labeling for INTRON A was amended to provide for 18-24 months of therapy. This revision was based on the findings of two studies that demonstrated an increased sustained end of follow-up ALT response in patients treated for 72 or 96 weeks. In these studies, a normalized ALT at week 16 of therapy was predictive of a sustained ALT response. Therefore, the labeling states that for patients who do not achieve an ALT response by week 16 of therapy, clinicians should consider discontinuing therapy.

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[4]NIH Consensus Development Conference Panel Statement. Management of hepatitis C. Hepatology 1997;26(Suppl 1):2S-10S.

Flu-like symptoms (fatigue, fever, headache and myalgia) are commonly reproted with INTRON A use. Myelosuppression has also occurred with the administration of INTRON A. INTRON A is an abortifacient. Psychiatric disorders including depression, emotional lability, suicidal ideation and successful suicides have been reported in patients receiving INTRON A.

3.3 International Marketing Experience

Ribavirin is approved as an aerosol, capsule, oral solution, syrup, injectable and topical cream formulations in 48 countries. Ribavirin is currently approved for the treatment of HCV infection in Mexico and Egypt. INTRON A® is approved in 69 countries, including the United States, for the treatment of HCV infection.

3.4 Clinical Implications of Preclinical Studies

3.4.1 Chemistry

Please refer to Dr. Kambhampati's review. There were no issues of clinical concern in the Chemistry Review.

3.4.2 Microbiology

Please refer to Dr. Batulla's review for information about the antiviral activity of INTRON A and ribavirin. Serum HCV-RNA levels were determined by a central laboratory using an experimental (research-based) assay. The lower limit of quantification for this assay was undefinable. Further, the mechanism of action of the INTRON A – ribavirin combination therapy against hepatitis C virus remains unknown.

3.4.3 Pharmacology/toxicology

Please refer to Dr. Morse's review. Ribavirin has been shown to be teratogenic and embryocidal in animal studies, and is considered a potential human carcinogen. The interferons are known abortofacients. The data provided in the NDA were not sufficient to address the concern of ribavirin's potential carcinogenicity. Therefore, additional, post-marketing, studies will be necessary. (See section 12.0).

3.4.4 Biopharmaceutics

Please refer to Dr. Rajagapolan's Clinical Pharmacology review for information about the effects of food on the bioavailability of ribavirin, and information about administration of ribavirin to patients with renal impairment. Further, no formal drug interaction studies have been performed.

4.0 Materials Reviewed

This NDA contains 294 volumes; of which 111 comprise the clinical section. All volumes of the clinical section of the NDA were reviewed in detail with the exception of the data devoted to assessment of quality-of-life. The quality-of-life data was primarily reviewed by the Division of Drug Marketing, Advertising and Communications.

The narratives and CRFs for deaths, serious adverse events and discontinuations that occurred in the two pivotal trials were reviewed. In addition, blinded safety data from two ongoing studies in interferon naïve patients and MedWatch forms for all deaths and serious adverse events that occurred during treatment and investigator-initiated protocols and open-label use were reviewed.

5.0 Summary of Clinical Section

Two trials were conducted in patients with chronic HCV infection with compensated liver function who had relapsed following a response to a previous course of interferon therapy. Both trials, C95-144 and I95-145, were identical in the protocol design, duration of treatment, drug dosages used, and endpoints measured. The location of the study centers differ; study C95-144 was conducted in the United States and I95-145 was conducted in Europe, Canada, Australia and Israel.

Table 1. Summary of submitted principal studies

Study	Location	Enrolled (N)	INTRON A + Ribavirin	INTRON A + Placebo
C95-144	21 US sites	154	77	76
I95-145	31 Foreign sites	195	96	96

To support the safety of this combination, the applicant has submitted complete safety data from the above two trials, blinded 24 week safety data from two ongoing trials in interferon naïve patients, and a review of serious adverse events and deaths that have occurred during Schering-controlled and investigator-initiated treatment protocols, and open-label use.

6.0 Clinical Trial C95-144

"Interferon Alfa-2B (INTRON A) monotherapy versus Interferon Alfa-2B (INTRON A) + Ribavirin (Sch 18908) for treatment of relapse in patients with chronic hepatitis C."

6.1 Study Design

This was a phase III, prospective, randomized, double-blinded study designed to compare the safety and efficacy of the combination of INTRON A + ribavirin to INTRON A + placebo in patients with chronic HCV infection in patients who had relapsed, based on abnormal ALT levels within one year after showing a response to 1 or 2 courses of alfa-interferon (3 MU to 6 MU QOD or TID for 20 weeks to 18 months).

The study population included 153 adult patients who were randomly assigned to receive INTRON A 3 MIU TIW + ribavirin 1,000 or 1,200 mg/day (n=77) or INTRON A 3 MIU TIW + placebo (n=76). The dose of ribavirin was based on weight; patients weighing ≥75 kg received 600 mg BID and those weighing <75 kg received 500 mg BID. Patients received treatment for 24 weeks followed by a 24-week off-therapy follow-up. The study was conducted between April 1, 1996 and October 27, 1997.

Comment: The dosing regimen of INTRON A used in this study was the licensed regimen at the time the study was initiated. The ribavirin dose was based on the maximally tolerated dose that had been used in previous monotherapy studies. Dose ranging studies requested by the agency are in progress.

During treatment and post-treatment follow-up, ALT and HCV-RNA levels were monitored serially. In addition, histopathologic comparisons of pre-treatment and post-treatment (obtained at week 48) liver biopsies were conducted by a central pathologist using components I+II+III of the Knodell Histology Activity Index[5] score. During the treatment phase, patients were assessed every 2 weeks for 8 weeks and

[5]The Knodell HAI composite score ranges from 0 to a maximum of 22. To obtain the composite score, liver biopsy is evaluated for periportal +/- bridging necrosis (category I), intralobular degeneration and focal necrosis (category II), portal inflammation (category III) and fibrosis (category IV). For each category, absence of activity, mild activity, moderate activity, and severe activity are attributed with numerical scores of 0, 1, 3, and 4, respectively. A score of 2 is not given. The composite score weighs heavily on category I (periportal +/- bridging hepatocellular necrosis) with maximum score of 10, whereas the highest scores for other categories are 4, since it appears that activity in this category best correlates with severity of disease. In grading category I, emphasis is placed on the severity of florid lobular necrosis, therefore, a score of 6 is given to marked piecemeal necrosis plus bridging necrosis and 10 for multilobular necrosis. Again there are no numerical scores of 7 to 9 given to this category. According to the authors of the HAI score, the composite score can be broken into individual components of necrosis (categories I, II),

every 4 weeks thereafter for clinical adverse events and laboratory safety tests. Similar assessments were conducted during post-treatment follow-up at weeks 4, 8, 12 and 24.

Inclusion Criteria
Patients were eligible for enrollment if they had a positive serum hepatitis C virus by quantitative RT-PCR assay, documented abnormal ALT levels (within 3 months of entry), and liver biopsy (within 6 months of entry) showing evidence consistent with chronic hepatitis. Other entry criteria included Hgb > 12 g/dL and 13 g/dL for females and males, respectively; WBC $\geq$3,000/mm^3; platelets $\geq$100,000/mm^3; PT $\leq$2 seconds prolonged compared to control; albumin $\geq$3.5 g/dL; indirect bilirubin $\leq$0.8 mg/dL; direct bilirubin $\leq$0.3 mg/dL; creatinine $\leq$1.4 mg/dL; fasting blood glucose $\leq$115 mg/dL (for non-diabetic patients); HbA_{1C} $\leq$8.5% (for diabetic patients); normal TSH level; ANA titer $\leq$1:160; normal AFP level or no evidence of hepatocellular carcinoma on ultrasound; negative HBsAg; negative HIV status; and adequate birth control practice.

Exclusion Criteria
Patients were excluded if they had other causes of liver disease, decompensated liver disease, were HIV or HBsAG positive. In addition, history of ribavirin use, active illicit intravenous drug use, pregnancy, breast-feeding, heavy alcohol consumption (>20 g/day), and participation on other investigational therapy were reasons for exclusion. Patients with a pre-existing psychiatric condition, especially severe depression or a history of severe psychiatric disorder; cardiovascular disorders including angina, congestive heart failure, recent myocardial infarction, severe hypertension, significant arrhythmias or an ECG showing clinically significant abnormalities; coexisting liver disease, and recipients of organ transplantation were not allowed to participate in this study.

Comment: The applicant enrolled a relatively healthy population of HCV infected patient with mild hepatic disease at entry who had all responded to a previous course of interferon monotherapy.

Randomization was stratified according to three criteria: presence or absence of cirrhosis, serum HCV-RNA greater or less than 2 x 10^6 copies/mL, and HCV genotype (genotype 1 or other).

6.2 Description of Study Population

6.2.1 Baseline Demographic Characteristics

The baseline demographic characteristics of patients enrolled in this study are summarized in Table 2.

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inflammation (category III), and fibrosis (category IV) for additional evaluation of the disease. (See Appendix A).

Table 2. Baseline Demographic Characteristics

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Age (years):		
- Mean	42.6	44.5
- Range	29-67	28-66
Gender:		
- Male	49 (64%)	53 (70%)
- Female	28 (36%)	23 (30%)
Race:		
- White	71 (92%)	69 (91%)
- Asian	1 (1%)	1 (1%)
- Black	1 (1%)	1 (1%)
- Hispanic	3 (4%)	5 (7%)
- Other	1 (1%)	-

Source: NDA 20-903, Protocol No. C95-145, Vols. 3.45, 3.50 and 3.51.

Comment: The baseline demographic characteristics of study patients were similar between the two treatment groups.

6.2.2 Baseline Disease Characteristics

The baseline disease characteristics of study participants are presented in Table 3.

Table 3. Baseline Disease Characteristics

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Source of Exposure:		
Transfusion	18 (23%)	21 (28%)
Parenteral	37 (48%)	43 (57%)
Sporadic/Other/Unknown	22 (29%)	12 (16%)
Years Since Exposure:		
Mean[1]	15	18.4
Range	1 - 37	2 - 37
HCV Genotype		
1 (total)	46 (60%)	42 (55%)
- 1a	21	13
- 1b	16	24
2 (total)	16 (21%)	17 (22%)
- 2a	3	1
- 2b	13	16
3a	15 (19%)	17 (22%)
4h	-	1 (1%)
HCV-RNA[2]		
$\leq 2 \times 10^6$ copies/mL	9 (12%)	12 (16%)
$>2 \times 10^6$ copies/mL	68 (88%)	64 (84%)
Mean	6.5×10^6	6.3×10^6
Knodell HAI score:		
Mean total score (I+II+III)	6.8	6.9
Mean fibrosis score (IV)	1.31	1.5
ALT (upper limit of normal):		
Mean	3.4	3.3
Range	1.4 - 13.2	1.1 - 8.2

Source: NDA 20-903, Study C95-144, Volume 3.45, and Appendix 12, Volumes 3.50 and 3.51.
1. Years since exposure was missing for 8 INTRON A + ribavirin and 9 INTRON A + placebo patients.
2. One INTRON A + ribavirin patient entered the study with a baseline HCV-RNA below LOQ of the assay

Comments: The baseline disease characteristics of the study population were well-balanced between the treatment groups. The baseline Knodell HAI scores reflected relatively mild histological disease in both treatment groups. Baseline fibrosis was also very low in study patients.

6.3 Evaluation Criteria

The applicant's primary endpoint was an overall response defined as serum HCV-RNA below the limit of quantification (LOQ) of the assay at 24 weeks of follow-up and improvement of liver biopsy by ≥ 2 points in the Knodell "inflammation" score (defined as the sum of category I, II and III scores) at week 48 (end of follow-up).

Comment: The original protocol-specified definition of a sustained virologic response was a virologic response at the end of treatment (week 24) maintained to the end of follow-up (week 48). During the conduct of the study, the applicant revised the definition of sustained virologic response to be HCV-RNA below the LOQ only at week 48. This change in definition could allow patients with detectable levels of HCV-RNA up to the last study visit to be considered sustained responders, and could have overestimated the true response rate. Therefore, the FDA used the original protocol-specified definition in the analyses of the data in this NDA.

Secondary endpoints included: (1) HCV-RNA responses at week 24 (end of treatment) and at week 48 (end of follow-up), (2) proportion of patients with normalization of ALT at weeks 24 and 48, (3) proportion of patients with overall improvement of liver biopsy findings (based on inflammation scores), and, (4) changes from baseline of liver biopsy scores.

Comments: The "inflammation" score, as defined by the applicant, reflected the sum of category I (periportal +/- bridging necrosis), II (intralobular degeneration and focal necrosis), and III (portal inflammation) scores. This "inflammation" score did not include category IV, i.e., the degree of fibrosis, which is a significant pathological feature of chronic HCV infection. Although somewhat arbitrary, the choice of a 2 point change in histology as a marker of improvement was agreed to because the applicant asserted that this magnitude of change was clinically relevant.

6.4 Patient Disposition

Overall, 82% of patients completed the study; 79% in the INTRON A + ribavirin group and 85.5% in the INTRON A + placebo group. Ten INTRON A + ribavirin and five of INTRON A + placebo recipients did not complete the 24 week treatment period. The primary reason for discontinuation during treatment was adverse events, seven and three in the INTRON A + ribavirin and INTRON A + placebo groups, respectively. The remaining patients who discontinued during the treatment period did so because they did not wish to continue (n=4) or due to noncompliance (n=1).

An additional four INTRON A + placebo patients completed 24 weeks of therapy but did not wish to enter the follow-up phase (n=3) or were lost-to-follow-up (n=1). In the INTRON A + ribavirin group, three patients completed the dosing period but either did not wish to continue with the follow-up period, were lost-to-follow-up or were non-compliant.

6.5 Protocol Violations

There were 33 cases of protocol violations with respect to entry inclusion/exclusion criteria. These cases are summarized in Table 4.

Table 4. Entry Criteria Protocol Violations

	INTRON A + Ribavirin	INTRON A – Placebo
Prior interferon <20 or >78 wks	1	1
Improper liver biopsy timing	2	3
Missing baseline liver biopsy	2	1
Indirect bilirubin >0.8 mg/dL	4	5
Fasting glucose >125 mg/dL	1	2
Neutrophils ≤1500/mm^3	1	2
Normal ALT (at baseline)		1
TSH <0.2 or >5.5	2	3
HCV-RNA <LOQ	1	
Misrandomized		1

Source: NDA 20-903. General Correspondence dated January 13, 1998, and Volumes 2.45, 2.50 and 2.51.

Comment: One patient in the INTRON A + ribavirin arm had a screening viral load value of 130,000 copies/mL. At the time of randomization, the patient's viral load was <100 copies/mL. Although it was unlikely that this patient had a virologic response to therapy, he was nonetheless included in all of the efficacy analyses. Otherwise, the entry inclusion/exclusion criteria violations did not appear to have compromised patient eligibility, safety, or had a significant impact on study treatment.

6.6 Efficacy Analysis

6.6.1 Virologic Response

The proportion of patients with HCV-RNA below the LOQ at each evaluation time point during the treatment period (weeks 4, 12, and 24) and during follow-up (weeks 36 and 48) are summarized in Table 5.

Table 5. Virologic Responses at Measured Time Points

	Treatment Period			Follow-Up Period	
	Week 4	Week 12	Week 24	Week 36	Week 48
INTRON A – Ribavirin (n=77)	31%	72%	71%	45%	43%
INTRON A + Placebo (n=76)	6.5%	29%	45%	5.2%	3.9%

The proportion of patients with sustained virologic response are presented in Table 6.

Table 6. Time to Sustained Virologic Response, N(%)

	INTRON A + Ribavirin	INTRON A – Placebo
Sustained response	33 (43)	3 (4)
Non-sustained response/missing	44 (57)	7 (96)
Time to sustained response		
-By week 4	18 (55)	3 (100)
-By week 12	33 (100)	-

Comment: Significantly more patients treated with INTRON A + ribavirin achieved a virologic response during treatment and maintained that response during the off-therapy follow-up period. In both treatment groups, all of the patients who were sustained virologic responders had achieved their initial virologic response by week 12.

The applicant stratified patients by baseline level of virus (≤ and >2 million copies mL). Analysis of virologic response based on this cut-off demonstrated that patients with ≤2 million copies/mL had a generally more favorable response to therapy than patients with higher baseline levels.

Comment: Baseline viral load was weakly correlated with sustained virologic response. Although the number of patients who entered the study with a baseline viral load of ≤2 million copes/mL was small, the results were consistent with reports that patients with lower baseline viral load levels tend to respond more favorably to therapy.

Genotypes 1, 2, and 3 are the most common HCV subtypes in patients from Europe and the United States. Genotypes 1a and 1b have been associated with poor interferon treatment response in previous studies. Among patients in INTRON A + ribavirin group, 28% (13/46) with genotype 1, 75% (12/16) with genotype 2 and 53% (8/15) with genotype 3 had sustained virologic responses. Among virologic non-responders, 71% (33/46), 25% (4/16) and 47% (7/15) had genotypes 1,2 or 3, respectively.

Of the three sustained virologic responders who received INTRON A + placebo, 2% (1/42) had genotype 1 and 12% (2/17) had genotype 3. Ninety-eight percent (41/42), 100% (17/17), 88% (15/17) and 100% (1/1) of virologic non-responders had genotypes 1, 2, 3, or 4, respectively.

Comment: Patients with genotype 1 virus had less favorable virologic response rates than patients with non-genotype 1 virus. The sustained response rate in INTRON A + ribavirin patients with genotype 1 virus was higher, 28%, compared to 2% in the INTRON A + placebo group. Thus, although patients with genotype 1 tend to respond less favorably than patients with non-genotype 1 virus, there did appear to be some benefit conveyed by the combination treatment.

6.6.2 Histologic Response

Complete sets of pre-treatment and end of follow-up biopsies were available for 62/77 (81%) and 64/76 (84%) of INTRON A + ribavirin and INTRON A + placebo patients, respectively. Histologic improvement rates for all study participants are presented in Table 7.

Table 7. Histologic Response Rates, N(%)

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Knodell I+II+III		
-Improvement	38 (50)	27 (36)
-No improvement worse	23 (30)	37 (49)
-Missing	16 (21)	12 (16)
Knodell I+II+III+IV		
-Improvement	39 (51)	27 (36)
-No improvement worse	22 (28)	37 (49)
-Missing	16 (21)	12 (16)

The mean histologic improvements in components I+II+III of the Knodell HAI score were 2.4 points and 0.7 points for patients in the INTRON A + ribavirin and INTRON A + placebo groups, respectively. When component IV (fibrosis) was included, the mean improvement remained 2.4 point and 0.6 points for the INTRON A + ribavirin and INTRON A + placebo groups, respectively.

Among sustained virologic responders the mean histologic improvement was 4.3 points (n=3) for the INTRON A + placebo-treated patients compared to 4.1 points (n=32) for INTRON A + ribavirin-treated patients. Improvement in HAI scores for virologic non-responders was ≤ 1 point in both treatment groups. Histologic improvements were primarily observed in components I, II, and III. The fibrosis score (component IV) did not show significant variations.

Comment: The number and reasons for missing end of follow-up biopsies were evenly distributed across the treatment arms and primarily reflected patient refusal to undergo a follow-up biopsy. Although component IV (fibrosis) is an important marker of disease status, its inclusion in the calculation of histologic change did not appreciably affect the results.

6.6.3 Overall Response

Overall response was defined as a HCV-RNA below LOQ at the end of follow-up combined with a ≥ 2 point improvement in components I+II+III of the HAI score on the post treatment liver biopsy compared to the pre-treatment biopsy. The applicant constructed a "maximum likelihood estimate" (MLE) so that patients whose overall response status could not be determined, i.e., patients with missing data, could contribute to the analysis. Using this procedure, the applicant determined that 36.5% of patients treated with INTRON A + ribavirin and 2.7% of patients treated with INTRON A + placebo successfully met the definition of the primary efficacy endpoint. The applicant also conducted an analysis that treated patients with either missing virologic or histologic data as treatment failures. This analysis demonstrated an overall response rate of 32.5% (25/77) and 2.6% (2/76) for the INTRON A + ribavirin and INTRON A + placebo arms, respectively.

The results of FDA's analyses were similar: 31% (24/77) in the INTRON A + ribavirin arm and 2.6% (2/76) in the INTRON A + placebo arm. The differences between the two analyses is a single patient who FDA considered a non virologic sustained responder.

The inclusion of component IV (fibrosis) in the calculation of histologic response affected one patient in the INTRON A + ribavirin arm of the study. By adding component IV, the magnitude of improvement in this patient's total HAI score was reduced from a 2 point improvement to a 0 point change, and would have lowered the overall response rate to 30% (23/77).

Comment: The applicant's and FDA's analyses yielded similar overall response rates and both analyses demonstrated an overall response in favor of the INTRON A + ribavirin combination. The overall response rates were significantly lower than what would be predicted by using either HCV-RNA or histology alone. There were no significant differences in outcomes for males compared to females.

6.6.4 Biochemical Response

ALT response rates at the end of therapy and at the end of follow-up were secondary endpoint measures. The results of this analysis, in addition to the proportion of patients who achieved a normal ALT at the end of therapy and maintained that normalization through the follow-up period are presented in Table 8.

Table 8. ALT Response Rates

	INTRON A + Ribavirin n=77	INTRON A + Placebo n=76
Normal at week 24	57 (74%)	37 (49%)
Normal at week 48	35 (45%)	11 (14%)
Normal at week 24 sustained through week 48	27 (35%)	3 (4%)

Of the 33 sustained virologic responders in the INTRON A + ribavirin arm, 24 (72%) also had sustained normalization of their ALT. Conversely, of the 38 patients who had improvement in histology, only 16 (42%) had normalization of their ALT levels.

Normalized ALT by week 4 was associated with a 56% likelihood of sustained virologic response. If normalization occurred at week 12, the likelihood of a sustained virologic response decreased to 32%. The likelihood of a sustained virologic response decrease to 20% if ALT normalization occurred at the week 24 measurement. A combined virologic response and ALT normalization by week 12 of therapy was associated with a 78% probability of sustained virologic response.

There was general agreement between histologic improvement and ALT normalization at week 48. Twenty seven of the 35 patients in the combination arm with normal ALT levels at week 48 also had improvement in liver histology.

Comment: There was a significantly higher ALT normalization rate in the INTRON A + ribavirin-treated patients compared to those treated with INTRON A + placebo. Although ALT levels were variable throughout the study period, there was high concordance between a sustained virologic response and normalization of ALT at week 48. There less concordance between normalization of ALT and improvements in liver histology.

6.6.5 Comparison of Responders and Non-Responders

A comparison of the characteristics of responders to INTRON A + ribavirin therapy compared to non-responders is provided in Table 9.

Table 9. Comparison of Responders and Non-Responders

Parameter	Overall Responders n=24	Non-Responders n=53
Age (years):		
Mean	40.2	43.8
Range	31 - 57	29 - 67
Gender:		
Male	13 (54%)	37 (72%)
Female	11 (46%)	15 (28%)
Source of exposure:		
Parenteral	13 (54%)	23 (45%)
Transfusion	4 (17%)	14 (26%)
Sporadic Other/Unknown	7 (29%)	15 (28%)
Years since exposure:		
Mean	14.4	15.0
Range	1 - 27	2 - 37
HCV Genotype:		
1	7 (29%)	39 (74%)
2	9 (38%)	7 (13%)
3a	8 (33%)	7 (13%)
Baseline HCV-RNA:		
Mean	6.6×10^6	7.1×10^6
Range	.1 - 20.1	.45 - 26.5
HCV-RNA		
≤ 2 million copies/mL	4	4
>2 million copies/mL	20	47
Mean baseline Knodell[1]	8.33	7.83
Mean baseline ALT (xULN)	5.45	0.54

1. For mean baseline Knodell score only 37 patients in the non-responder category had matched sets of pre- and post-study biopsies.

Comment: Although there were more males than females enrolled in the study, females had a slightly better overall responses to therapy. Patients with Genotype 1 responded less often than patients with other genotypes. A baseline viral load of ≤2 million copies/mL appeared to have a weak association with overall response (p=0.25), but, as noted above, the number of patients with this baseline HCV-RNA level was small. In general, it appears that neither baseline viral load, baseline ALT levels or baseline HAI scores were good predictors of response.

6.7 Safety Analysis

All patients in this study were included in the analysis of safety.

6.7.1 Deaths

There were no deaths reported during this study.

6.7.2 Dose Modifications Due to Adverse Events

During the 24-week dosing period, 34% (27/77) of INTRON A + ribavirin-treated patients underwent a dose modification (reduction, interruption, or both) because of an adverse event compared to 17% (13/76) in the INTRON A – placebo group.

Table 10. Dose Modifications Due to Adverse Events

	INTRON A + Ribavirin	INTRON A + Placebo
Neutropenia	4	3
Anemia	6	
GI disorders	3	1
Musculoskeletal pain	3	1
Hyperthyroidism	3	
Dyspnea	2	
Psychiatric-related events	2	1
Elevated bilirubin	1	
Edema	1	
Flu-like symptoms		1
Malaise		1

Eight INTRON A – ribavirin patients and one INTRON A + placebo patient discontinued the study after dose modification because of adverse events. (See section 6.7.4).

Comment: The reasons for dose modifications were associated with known complications of INTRON A and ribavirin therapy.

6.7.3 Serious Adverse Events

Serious adverse events occurred in nine patients, five in the INTRON A – ribavirin arm and four in the INTRON A – placebo arm. The events in the INTRON A + ribavirin arm included: two injuries, one Bell's palsy, one hyperthyroidism and one suicide attempt. One case each of pyelonephritis, back injury, dehydration, and headache occurred in the INTRON A + placebo arm.

6.7.4 Adverse Events Associated with Premature Study Discontinuation

Ten patients discontinued the study, seven in the INTRON A + ribavirin group and three in the INTRON A + placebo group. The events leading to study discontinuation in the INTRON A + ribavirin group included one case of hyperthyroidism, two cases of depression with one suicide attempt, two cases of neutropenia, one case of arthralgias, and one case of arthralgias and emotional lability (mood swings). Nausea, vomiting and dehydration in two patients with pre-existing gastrointestinal disease and worsening musculoskeletal pain in one patient accounted for the three study drug discontinuations in the INTRON A + placebo arm.

Comment: A review of the CRFs supported the conclusion that the events leading to study discontinuation were generally consistent with the adverse events associated with INTRON A.

6.7.5 Clinically Important Adverse Events

Psychiatric-Related Events

Treatment emergent psychiatric adverse events, including depression, agitation, anxiety, mood swings, emotional lability, and impaired concentration occurred in 47 (61%) INTRON A + ribavirin patients and 36 (47%) INTRON A + placebo patients. As described above three patients in the INTRON A + ribavirin group discontinued the study due to psychiatric-related adverse events.

Treatment-emergent depression occurred in 23% (18/77) and 16% (12/76) of patients in the INTRON A + ribavirin and INTRON A + placebo arms, respectively. Table 12 summarizes the incidence and outcomes of depression that occurred during the 24 weeks of treatment in this trial.

Table 11. Treatment-Emergent Depression

	INTRON A + ribavirin (n=18)	INTRON A + placebo (n=12)
Median time to onset	Treatment week 4	Treatment week 8
Median time to resolution	Follow-up week 8	Treatment week 24
Received changed treatment	10	6
Suicide attempts	1	0

Five of the 18 INTRON A + ribavirin patients continued to have depression listed as an adverse event at end of study: three of these patients continued to receive antidepressant therapy as they exited the study. Only one INTRON A + placebo patient continued to have depression at the end of the study, but this patient discontinued antidepressant therapy during week 12 of follow-up.

The one attempted suicide that occurred in INTRON A + ribavirin group (#24-003) was in a 34 year old female with a history of intravenous drug abuse and alcohol abuse, but no prior history of depression. The patient experienced the onset of treatment emergent depression during treatment week 12 and was treated with Trazadone. During week 20 (approximately day 155) the patient attempted suicide. According to the applicant, the patient had reported that she had discontinued study medications approximately four weeks prior to the suicide attempt.

Comment: The incidence of treatment-emergent depression in this study was generally consistent with the rates reported in patients with chronic hepatitis C undergoing INTRON A monotherapy, approximately 19%.

Pregnancies

Ribavirin has been demonstrated to be teratogenic and embryocidal in animal studies and the interferons are known abortifacients. Two pregnancies were reported in this study. The first pregnancy occurred in the spouse of a patient who was receiving INTRON A + placebo; the pregnancy resulted in delivery of a

healthy full-term baby. The second pregnancy was in the spouse of a patient randomized to INTRON A – ribavirin; the outcome of this pregnancy is currently unknown.

Chest Pain

Chest pain, chest pain with palpitations or with tachycardia, was reported in 11 patients, six (8%) and five (6.5%) in the INTRON A + ribavirin and INTRON A – placebo arms, respectively. Four of the patients in the INTRON A – ribavirin arm had a concomitant reduction in their hemoglobin levels ranging from 1.9 g/dL to 4.1 g/dL. Three of the five INTRON A + placebo patients had decreases in their hemoglobin ranging from 0.7 g/dL to 1.7 g/dL. No patients underwent a dose modification or reduction because of a cardiac-related event.

Comment: Cardiac-related events associated with the use of INTRON A + ribavirin may not generalize to populations that include patients with pre-existing severe cardiac disease.

Dyspnea

Dyspnea was reported in 17% (13/77) INTRON A + ribavirin-treated patients and 12% (9/76) in INTRON A + placebo-treated patients. Twelve of the 13 INTRON A + ribavirin patients had concomitant reductions in their hemoglobin levels, with a maximum reduction in hemoglobin from baseline ranging between 1.9 - 5.0 g/dL. Only five patients in the INTRON A + placebo group had a concomitant reduction in hemoglobin from baseline; range 0.3 - 2.8 g/dL.

Two patients in the INTRON A + ribavirin arm had their dose of INTRON A reduced because of dyspnea. Both patients recovered and completed the study.

Comment: Dyspnea associated with anemia was more prevalent in the INTRON A – ribavirin group implying that ribavirin may have increased the severity of this adverse event.

Thyroid-Related Events

In the INTRON A – ribavirin patients, clinically significant elevations of TSH occurred in six patients during the 24 week dosing period. The elevations ranged from a low of 13.3 MIU/L to a high of 114 MIU/L. Three of these patients had a history of hypothyroidism at study entry, two of which had been receiving supplemental thyroid therapy. Treatment was initiated or modified in four of the six, and the other two patients did not receive therapy. In all six, TSH levels returned to normal or near-normal by week 12 of follow-up.

One INTRON A – ribavirin patient (#33-007) discontinued the study due to clinical events associated with hyperthyroidism. This patient entered the study with a TSH of 1.5 MIU/L, which subsequently decreased to 0.07 MIU/L during treatment week 12. During this period the patient complained of tachycardia and palpitations. His study medications were discontinued during treatment week 16.

Clinically significant elevations in TSH levels occurred in two INTRON A + placebo patients at the end of treatment; one each to 67 MIU/L and 23.3 MIU/L. Both patients entered the study with a history of hypothyroidism, both were receiving thyroid-related medications, both had modifications of their thyroid medications during the study, and both had their TSH subsequently return to normal levels by the 24 week follow-up visit.

Conversely, decreases in TSH levels below 0.2 MIU/L (lower limit for study inclusion) occurred during the 24-week treatment period in nine INTRON A + ribavirin and three INTRON A – placebo patients. Two of the INTRON A – placebo patients entered the study with a history of hypothyroidism on synthroid treatment. Neither patient had a change in their thyroid therapy, and both had subsequent normalization of their TSH levels by their next scheduled visit. The third INTRON A + placebo patient had a reduction in his TSH to 0.01 MIU/L at the week 24 visit. The patient did not enter the follow-up period so it is unknown if his hypothyroidism resolved.

Comment: Thyroid dysfunction occurred more frequently in patients with underlying thyroid disease. These events were generally treated by the addition or adjustments of thyroid medications. Only one patient in the INTRON A + ribavirin group discontinued due to tachycardia associated with hyperthyroidism.

6.7.6 Laboratory Abnormalities

Hemoglobin Levels

No INTRON A – placebo-treated patient had a reduction in hemoglobin to below 11.5 g/dL, and no patient in this group underwent dose modification.

The mean maximum hemoglobin decrease was 2.8 g/dL in the INTRON A + ribavirin arm compared to <1 g/dL in the INTRON A + placebo arm. Hemoglobin levels began to drop during week 1 and stabilized by week 4.

Overall, 75% (58/77) of INTRON A + ribavirin-treated patients had reductions in hemoglobin ≥2 g/dL from baseline compared to 8% (6/76) in the INTRON A – placebo arm. Nine of the INTRON A – ribavirin patients had a reduction from baseline between 4 and 6 g/dL, eight of which had reductions to below 10 g/dL, the level at which dose modifications were to occur.

Dose reductions of ribavirin for low hemoglobin levels was instituted for six of these patients. Hemoglobin levels returned to pre-treatment levels between 4 to 8 weeks following cessation of ribavirin therapy.

Comment: Anemia was very common in the INTRON A – ribavirin group. Anemia occurred in a relatively short period of time (within 1-2 weeks), stabilized by week 4 and generally returned to normal levels within 4-8 weeks following cessation of ribavirin therapy.

Platelet Counts

Treatment with INTRON A – ribavirin had little effect on platelet counts. The mean baseline platelet counts were the same in both treatment groups (202 x 10^9/L). The mean nadir platelet count in the INTRON A – ribavirin group was 164 x 10^9/L compared to 144 x 10^9/L in the INTRON A + placebo group.

Absolute reductions in platelet counts to ≤150,000/mm^3 occurred in four (5%) INTRON A + ribavirin patients and 13 (17%) INTRON A + placebo patients during the 24 week treatment period. No patient in this study had a dose modification, reduction, or discontinued study medication due to a decrease in platelet count.

Comment: Ribavirin treatment did not appear to influence the incidence of thrombocytopenia in study patients.

White Blood Cell counts

The mean WBC count was slightly lower in the INTRON A + ribavirin arm at week 4 compared to the INTRON A – placebo arm, 4.1 versus 4.6 x 10^9/L, respectively. Most of the WBC counts returned to normal levels within 4 weeks following cessation of therapy.

The mean baseline absolute neutrophil count (ANC) were similar between the treatment groups, 3.2 x 10^9/L in the INTRON A + ribavirin arm and 3.5 x 10^9/L in the INTRON A + placebo arm. The mean maximum ANC reductions during the treatment period were 1.9 x 10^9/L and 2.1 x 10^9/L in the INTRON A + ribavirin and INTRON A – placebo arms, respectively.

Thirteen INTRON A + ribavirin patients (17%) had reductions in their neutrophil counts to < 750/mm^3 during the treatment period. Four patients underwent a dose modification of ribavirin or INTRON A, or both, with subsequent recovery of their ANC; seven had no change in their study medications; and, two discontinued the study due to neutropenia. In the INTRON A + placebo group, 11 patients (14%) had reductions in ANC below 750/mm^3; only three underwent dose modifications. No INTRON A – placebo-treated patients discontinued therapy due to neutropenia.

Comment: The addition of ribavirin did not appear to potentiate the neutropenic effects of INTRON A.

6.7.7 All Adverse Events

Adverse events were reported by 100% of INTRON A – ribavirin and 99% of INTRON A + placebo treated patients during the 24-week dosing period. The most commonly reported adverse events are presented in Table 12.

Table 12. Selected Treatment Emergent Adverse Events (all grades)

Adverse Event	INTRON A – Ribavirin n (%)	INTRON A + Placebo n (%)
Asthenia	8 (10)	3 (4)
Chest pain	5 (6)	5 (7)
Edema	3 (4)	3 (4)
Fatigue	46 (60)	40 (53)
Fever	25 (32)	27 (36)
Headache	51 (66)	52 (68)
Rigors	33 (43)	28 (37)
Dizziness	20 (26)	16 (21)
Abdominal pain	13 (17)	19 (25)
Anorexia	16 (21)	11 (14)
Diarrhea	13 (17)	19 (25)
Dyspepsia	12 (16)	7 (9)
Nausea	36 (47)	25 (33)
Vomiting	9 (12)	6 (8)
Arthralgia	22 (29)	22 (29)
Musculo-skeletal pain	17 (22)	21 (28)
Myalgia	47 (61)	44 (58)
Anxiety	7 (9)	7 (9)
Concentration impaired	8 (10)	9 (12)
Depression	18 (23)	12 (16)
Emotional lability	9 (12)	6 (8)
Insomnia	20 (26)	19 (25)
Irritability	19 (25)	15 (20)
Infection-viral	10 (13)	8 (11)
Pruritis	10 (13)	3 (4)
Alopecia	21 (27)	20 (26)
Rash	16 (21)	4 (5)
Dyspnea	13 (17)	9 (12)
Flu-like symptoms	10 (13)	10 (13)

Source: NDA 20-903, Volume 3.45

Comment: Depression, pruritis, nausea, and rash occurred somewhat more frequently in the INTRON A + ribavirin treatment arm. There were three cases of neutropenia, two in the INTRON A + ribavirin arm and one in the INTRON A + placebo arm that were considered "life-threatening." There were no gender differences in types or frequencies of adverse events noted.

6.8 Assessment of Safety and Efficacy Based on Study C95-144

6.8.1 Efficacy

Evidence of efficacy was supported by greater virologic and histologic responses in patients treated with INTRON A + ribavirin compared to INTRON A + placebo.

Seventy-five percent of INTRON A + ribavirin-treated patients compared to 45% of INTRON A + placebo-treated patients achieved a virologic response by the end of treatment; however, only 43% and 4% sustained the response throughout the follow-up period. All of the patients who demonstrated a sustained virologic response achieved their initial virologic response by week 12.

Histologic improvement in the INTRON A + ribavirin group was somewhat higher than in the INTRON A + placebo-treated group 49% compared to 36%, respectively. The inclusion of component IV (fibrosis) in the analysis of histology did not impact the outcomes in this study. There were too few numbers of patients with cirrhosis at baseline to assess the impact of therapy on this parameter. Virologic responders had greater improvements in liver histology compared to virologic non-responders.

ALT levels were variable throughout the study. ALT normalization occurred in a significantly higher proportion of patients treated with INTRON A + ribavirin compared to INTRON A + placebo-treated patients. There was a high correlation between an end of follow-up HCV-RNA level below LOQ and normal ALT levels. Patients with both a virologic response and normalization of ALT by week 4, or virologic response by week 4 alone, had a higher probability of a sustained virologic response than those who only achieved an ALT response at week 4. Finally, normal ALT levels at week 48 were generally associated with improvements in liver histology.

Patients with non-genotype 1 virus responded better than patients with genotype 1 regardless of treatment received. Patients with baseline viral loads of ≤ 2 million copies/mL appeared to have a more favorable response than patients with higher baseline levels. However, there were very few patients with baseline levels below 2 million to support a treatment decision. When analyzed together, lower baseline viral load and non-genotype 1 were weakly correlated with an improved virologic response to therapy.

This study failed to clearly identify a specific patient population that were likely to have a high response to therapy. In general, male patients and patients with Genotype 1 generally had less favorable responses to therapy. Baseline viral load, baseline HAI score and baseline line ALT levels were not predictive of a response to therapy.

To conclude, the results of this study demonstrated a short-term benefit for patients treated with the combination compared to those re-treated with interferon monotherapy. In general, sustained virologic response was associated with normalization of ALT levels and improvements in liver histology.

6.8.2 Safety

No deaths occurred in this study. A similar number of patients in both treatment groups required dose modifications because of neutropenia and psychiatric-related events. Dose modifications due to anemia (reductions in hemoglobin) occurred only in the INTRON A + ribavirin group.

A higher number of patients in the INTRON A + ribavirin group experienced serious and life-threatening adverse events including neutropenia, depression, including one attempted suicide, and thyroid dysfunctions than the INTRON A + placebo group.

Patients with significant underlying psychiatric disorders at baseline were excluded from the study. Overall, 62% of study participants experienced a psychiatric-related event: irritability, depression and insomnia being the most common events. The incidence of treatment-emergent depression in this study was common but generally consistent with the incidence of depression reported in previous studies of INTRON A. One patient in the INTRON A + ribavirin group who became depressed on therapy attempted suicide.

Ribavirin induced anemia occurred in the majority of patients, with over 70% of combination treated patients having a ≥2 g/dL reduction in hemoglobin from baseline. The onset of anemia was rapid, within the first 1-2 weeks of therapy. Anemia was generally reversible following cessation of treatment. Increased rates of chest pain and dyspnea occurred in some patients treated with INTRON A + ribavirin, and in some cases these events were associated with reductions in hemoglobin levels. Patients with severe pre-existing cardiovascular disease were excluded from entry into this study.

Neutropenia occurred in similar numbers of patients in both treatment groups. However, more patients in the INTRON A – ribavirin group underwent a dose modification or discontinued therapy due to neutropenia. A higher proportion of patients in the INTRON A + placebo group had reductions in their platelet counts.

Other reported adverse events were very common in both treatment groups, the majority of which were of mild to moderate severity. Overall, the adverse events seen in this study were similar to those associated with the use of INTRON A. There was no apparent differences in the types or frequency of adverse events seen in females compared to males. With the exception of anemia, it did not appear that the addition of ribavirin potentiated the laboratory abnormalities seen in this study.

The types of adverse events in this study were consistent with the known safety profiles of INTRON A and ribavirin; however, most were reported more frequently in the combination arm. The primary toxicities of concern included anemia and depression.

7.0 Clinical Trial I95-145

"Interferon Alfa-2B (INTRON A) monotherapy versus Interferon Alfa-2B (INTRON A) + Ribavirin (Sch 18908) for treatment of relapse in patients with chronic hepatitis C." For a comprehensive review of this study, please see the review by Dr. Tan Nguyen that is appended to this review (See Appendix B).

This was a second phase III, prospective, randomized, double-blinded study of 192 HCV infected patients designed to compare the safety and efficacy of the combination of INTRON A + ribavirin to INTRON A + placebo. The study inclusion/exclusion criteria, dosing regimens, evaluation criteria were the same as in study C95-144. The efficacy and safety findings of study I95-145 were generally consistent with the results of study C95-144.

The efficacy analyses demonstrated:

- a sustained virologic response of 47% in the INTRON A + ribavirin group compared to 5% in the INTRON A – placebo arm;
- a higher rate of histologic response in virologic responders;
- an overall response to therapy of 36.5% and 4.2% in INTRON A + ribavirin and INTRON A + placebo-treated patients, repsectively; and
- most patients who achieved a virologc response also had normalization of their ALT levels.

The types of adverse events were also similar between the two studies with psychiatric events and anemia occurring frequently. Of note, however, the reported frequency of events were generally lower in this trial. The lower reporting appears to be consistent with a general lower reporting by non-US investigators

8.0 Supportive Safety Data

In addition to complete safety data from the two phase 3 trials, the applicant has submitted interim blinded safety data from approximately 1744 patients currently enrolled in two ongoing double-blind, randomized trials of INTRON A + placebo or ribavirin in patients naïve to INTRON A, and serious adverse events and deaths among approximately 30,000 patients receiving treatment under other Schering-sponsored studies (n≈2,100), investigator-initiated studies (n≈2,600), and open-label and expanded use (n≈25,000). A review of these data is presented below.

8.1 Clinical Trials C95-132 and I95-143

The applicant has provided blinded safety data from two ongoing trials that compare combination therapy of INTRON A + ribavirin with INTRON A + placebo in patients who have not previously received INTRON A. Patients in these trials were randomly assigned to receive Intron A 3 MIU TIW plus ribavirin 1000 or 1200 mg/day (n=1010) or Intron A 3 MIU TIW plus placebo (n=734) for either 24 or 48 (n=915) weeks followed by a 24 week off therapy follow-up period. The reporting period for these studies is August 1, 1995 though January 28, 1998.

8.1.1 Deaths

Five deaths have occurred in the two naïve studies.

Two deaths due to myocardial infarctions occurred during the first 24 weeks of study C95-132. The first death (patient #15-039) occurred in a 56 year old black male with a history of diabetes, angina, hypertension and previous myocardial infarction. Four weeks prior to death the patient had a 6 g dL reduction from baseline in his hemoglobin to 9.6 g dL. The dose of ribavirin was reduced but his hemoglobin remained low (between 10.3 g/dL and 9.3 g/dL). The patient had an acute myocardial infarction and died during treatment week 20.

The second cardiac-related death (patient #39-012) occurred in a 59 year old caucasian male with a history of hypertension and diabetes. Approximately treatment week 20, the patient had an acute inferior wall and right ventricular myocardial infarction. Cardiac catheterization revealed triple vessel disease. The patient underwent coronary artery bypass surgery, but died during surgery. This patient had a reduction in hemoglobin from a baseline of 16.5 g/dL to 13.2 g/dL at the time of death. This patient was receiving INTRON A – placebo.

Two deaths due to illicit drug overdoses occurred in study C95-132. The first death (patient #35-002) occurred during follow-up week 16 in a 43 year old male patient with a history of illicit drug use and depression. This patient had successfully completed 48 weeks of blinded study medication. The other drug overdose occurred in patient #44-019. This patient was a 43 year old female with a history of mild depression who died of an "accidental" overdose while in her 36th week of receiving blinded study medication.

The one death in study I95-143 (patient #25-005) occurred during follow-up week 20 and was due to an intracranial hemorrhage secondary to a fall.

Comment: Both deaths due to myocardial infarctions occurred in patients with pre-existing cardiovascular disease and diabetes. Both deaths due to drug overdoses occurred in patients with pre-existing depression. These deaths were possibly associated with study medication. The death due to intracranial hemorrhage was not attributable to study medication.

8.1.2 Serious Adverse Events

A total of 202 patients reported 370 serious adverse events during the 24-week treatment or follow-up period. The most commonly reported events included: hepatic neoplasms (2), chest pain (10), myocardial infarction (6), angina (3), hypertension (2), fever (12), anemia (2), thyroid dysfunction (16), abdominal pain (17), vomiting (13), pneumonia (5), depression (5), hallucinations (4), anxiety (4), suicidal ideation (6), suicide attempt (8), aggressive reaction (5), and dyspnea (6).

Comment: The types of serious adverse events listed herein are, again, consistent with the adverse event profiles seen with the use of INTRON A and ribavirin in the relapse studies reviewed above. The events remain blinded to study treatment.

8.1.3 Withdrawals for Adverse Events

According to the applicant, 137 (8%) patients discontinued the studies during the first 24 weeks of dosing because of adverse events. A total of 109 discontinued study medication due to a psychiatric-related event, including: depression (26), suicidal ideation (7), suicide attempt (2), anxiety (5), emotional lability (3), aggressive behavior (2), insomnia (1), irritability (4), abnormal thinking (1), impaired concentration (1), neurosis (1), agitation (1) or hallucinations (1).

There were eight patients who discontinued study medication due to a cardiac-related adverse event, i.e., chest pain angina, myocardial infarction or cardiac failure.

Comment: The treatment arms remain blinded. Serious cardiac-related events and serious psychiatric-related events (anxiety, depression, suicidal ideation and attempts) were the most common reason for study drug discontinuation. There were no unexpected events leading to study discontinuation.

8.1.4 Pregnancies

Nineteen pregnancies have been reported between the two naïve patient trials; seven in patients and 12 in partners. The outcomes of these pregnancies include: miscarriage (9), voluntary termination (3), delivery of a healthy baby (2), and unknown (5). The patients' treatment assignment remains blinded.

8.1.5 All Adverse Events

Adverse events were reported by 98% of INTRON A – ribavirin and 99% of INTRON A + placebo patients during the first 24 weeks of the study. The most commonly occurring adverse events are presented in Table 13.

Table 13. Selected Treatment Emergent Adverse Events (all grades)

Event	INTRON A + Ribavirin n (%)	INTRON A + Placebo n (%)
Application site disorders	122 (12)	121 (16)
Asthenia	195 (19)	102 (14)
Chest pain	39 (4)	28 (4)
Fatigue	528 (52)	415 (55)
Fever	336 (33)	255 (35)
Headache	579 (57)	439 (60)
Rigors	276 (27)	198 (27)
Dizziness	133 (13)	92 (13)
Abdominal pain	123 (12)	113 (15)
Anorexia	211 (21)	115 (16)
Diarrhea	153 (15)	141 (19)
Dyspepsia	95 (9)	45 (6)
Nausea	315 (31)	195 (27)
Vomiting	76 (8)	63 (9)
Arthralgia	233 (23)	197 (27)
Musculoskeletal pain	207 (20)	172 (23)
Myalgia	460 (46)	369 (50)
Anxiety	93 (9)	61 (8)
Concentration impaired	87 (9)	73 (10)
Depression	234 (23)	163 (22)
Emotional lability	64 (6)	42 (5)
Insomnia	312 (31)	166 (23)
Irritability	184 (18)	119 (16)
Infection-viral	104 (10)	78 (11)
Pruritis	186 (18)	53 (7)
Alopecia	242 (24)	184 (25)
Rash	157 (16)	48 (7)
Dyspnea	142 (14)	53 (7)
Flu-like symptoms	250 (25)	184 (25)
Anemia	75 (7)	1 (<1)

Source: NDA 20-903, Volume 3.75, Attachment 10 and 11

Comment: Overall, the types and frequency of adverse events were similar to those reported in the relapse studies reviewed above.

8.2 Treatment Protocols/Investigator-Initiated Studies/Open-Label Use

Approximately 25,000 patients have received ribavirin either alone or in combination with interferon in Schering-controlled treatment protocols, investigator-initiated studies, or in worldwide open-label use between August 1, 1995 and January 28, 1998.

8.2.1 Deaths

A total of 17 deaths have been reported in this patient population. Each death is summarized below.

- A suicide occurred in a 51 year old male in a treatment protocol who was receiving re-treatment with INTRON A + ribavirin following a relapse of his HCV after a previous course of interferon monotherapy. The patient experienced anxiety but had not exhibited any overt depressive symptoms.

He committed suicide by drowning himself approximately one month after initiating combination therapy.

- A 56 year old male in a treatment protocol committed suicide approximately 11 months after starting INTRON A + ribavirin. At the time of death, the investigator noted that the patient was exhibiting depressive symptoms. The patient had no previous history of depression.

- A literature report of a 58 year old male who was receiving interferon + ribavirin for relapse of HCV following orthotopic liver transplantation at the time of death. The patient was reportedly non-compliant with his medications and died from complications associated with chronic rejection.

- A 34 year old male died suddenly during the screening phase of a treatment protocol. The patient had not yet received either interferon or ribavirin. The cause of death was not determined.

- A 46 year old female died due to purulent meningitis possibly secondary to metastases from hepatocellular carcinoma. The patient was receiving ribavirin monotherapy as part of a treatment protocol at the time of death.

- A 68 year old male received ribavirin monotherapy for 5 months. Approximately four weeks after cessation of ribavirin therapy the patient died of cardiac failure associated with liver failure. This patient had both chronic HCV and cirrhosis.

- A 34 year old male who received open-label INTRON A + ribavirin died of a subarachnoid hemorrhage due to a ruptured congenital aneurysm. The patient had been receiving INTRON A + ribavirin treatment for approximately two months prior to death.

- A 42 year old female died due to gastrointestinal hemorrhage and thrombocytopenia (platelet counts not provided). The patient was receiving open-label ribavirin with Roferon at the time of her death.

- A 59 year old male died of cardiac failure. While receiving INTRON A + ribavirin, the patient had episodes of neutropenia (ANC 0.7), feeling "down in the dumps" and hearing voices. The patient was admitted because of fever, chills and a productive cough and pneumonia. The next morning he was found unconscious; resuscitative efforts failed and the patient died.

- A 55 year old male died of septic shock and renal and liver failure. The patient was off of INTRON A + ribavirin therapy for over one year at the time of his death.

- A 55 year old female with a history of hypertension received therapy with INTRON A + ribavirin under a treatment protocol. Seventeen weeks after initiating therapy the patient complained of shortness of breath, hemoptysis and left-sided pleuritic chest pain. Pulmonary infiltrates were found on chest x-ray. She died approximately two weeks later of a pneumonia (type unknown).

- A 59 year old male died of cardiac arrest approximately one month after commencing Roferon and open-label ribavirin. The patient had a history of ischemic cardiomyopathy and had undergone a coronary artery bypass approximately 8 years prior to death.

- A 47 year old male experienced sudden death due to a coronary thrombosis approximately four weeks after cessation of open-label INTRON A + ribavirin therapy. This patient had no prior history of cardiovascular disease.

- A 65 year old male with poorly controlled hypertension initiated open-label Intron A + ribavirin therapy in January 1997. In January 1998, the patient died of a massive cerebral hemorrhage.

- A 20 year old male in a treatment protocol died from injuries suffered in an automobile accident.

- A 42 year old male who received INTRON A + ribavirin in a treatment protocol died suddenly approximately one month following discontinuation of therapy. The cause of death was reported to be a methadone overdose.

- A 73 year old female died of a presumed cardiac arrhythmia approximately five moths following cessation of INTRON A + open-label ribavirin therapy.

Comment: Six on-therapy deaths were possibly associated with use of ribavirin and/or interferon: two suicides, one cardiac arrest in a patient with a cardiac history, two pneumonias, and one hemorrhage with concomitant thrombocytopenia.

8.2.2 Serious Adverse Events

Serious psychiatric events including depression, suicidal ideation, suicide attempts, successful (accomplished) suicides, aggressive reactions, agitation, anxiety, emotional lability, hallucinations, nervousness, paranoid reaction, schizophrenia, psychoses, insomnia, and irritability were reported during investigator-initiated and other treatment protocols.

The serious cardiovascular adverse events most often reported were: myocardial infarction, angina, cardiac arrest/failure, palpitations, hypertension, hypotension, arrhythmia, and pericardial effusions. Dyspnea was also a reported serious adverse event.

Hemoglobinemia, granulocytopenia and thrombocytopenia were reported serious hematological events reported.

Comment: There were no unexpected serious adverse events reported. Given the combination of controlled and uncontrolled use of interferon and ribavirin in this patient population, the incidence rate of any one event or a group of associated events cannot be calculated with confidence.

8.2.3 Pregnancies

Seven pregnancies were reported in patients (4) or their partners (3). Two patients and three partners became pregnant while one of the pair was receiving INTRON A + ribavirin. Two pregnancies ended in miscarriages and the outcomes for the other three are unknown. One patient became pregnant during the screening period for an individual-investigator study and had a voluntary termination of the pregnancy. The seventh patient had a miscarriage four weeks after receiving ribavirin in a single-dose pharmacokinetics study.

9.0 Overall Summary of Efficacy and Safety

9.1 Efficacy

The results of two double-blind, randomized, controlled trials were submitted by the applicant to support of the efficacy of INTRON A + ribavirin in the treatment of chronic HCV infection in patients who had relapsed following a response to previous interferon therapy. A total of 345 patients were randomized to receive INTRON A + ribavirin or INTRON A + placebo for 24 weeks followed by a 24 week off-therapy follow-up period. Efficacy analyses were based on sustained virological response, improvements in liver histology, and an overall response endpoint that combined both these parameters.

The results of these studies demonstrated that:

- Treatment with INTRON A + ribavirin resulted in significantly greater sustained virologic responses compared to INTRON A + placebo. It appeared that patients who did not achieve a virologic response by week 12 of therapy did not achieve a sustained virologic response.

- Although liver biopsies are associated with a certain amount of morbidity, the applicant was able to obtain complete pre- and post-study biopsy sets in 80% of study participants. Treatment with the INTRON A – ribavirin resulted in higher histologic improvement rates across the two studies compared to treatment with INTRON A – placebo. 50% versus 33%.

- Overall response rates were also similar across the two studies. In study 144, overall response to therapy was 31% and 2.6% in the INTRON A + ribavirin and INTRON A + placebo groups, respectively. In study 145, the rates were 35% and 4.2%. When the overall response results from both studies are combined, patients treated with INTRON A + ribavirin demonstrated a 10-fold greater response (33%) compared to patients treated with INTRON A + placebo (3%). Further, a sustained virologic response was associated with higher improvements in liver histology.

- ALT levels were variable throughout the study period but were well correlated with end of study HCV-RNA values. Patients with normal ALT values at week 48 generally also had an HCV-RNA below the LOQ at week 48. There appeared to be less correlation between normalization of ALT at week 48 and improvements in biopsy scores.

Dose
The regimen of INTRON A chosen for this trial was the licensed regimen at the time the studies were initiated. The dose of ribavirin was based on the maximum tolerated dose identified early in the drugs' development and used in previous monotherapy studies. The applicant has not completed any dose ranging studies to determine if lower doses of ribavirin might have achieved similar or better response rate.

Duration
The applicant submitted data from six months of therapy with six months of post-therapy follow-up. There are currently no data to support the safety or efficacy of shorter or longer treatment regimens with this combination. In both studies, time to initial virologic response was predictive of sustained virological response. Specifically, all of the patients who were sustained virologic responders had achieved their initial response by week 12 of therapy.

Parameters of response
HCV-RNA is emerging as a primary parameter for following patient responses to therapy. Although the assay used in these trials was able to detect the presence or absence of HCV-RNA reasonably well, the LOQ of the assay used in these trials could not be fully validated. Therefore, it is not yet possible to endorse the use of HCV-RNA as the sole measure of response.

The clinical relevance of small improvements in the inflammatory score components of the Knodell system are unknown given the problems with of sampling inherent in liver biopsy specimens, as well as inter-reader variability. The choice of a $\geq$2 point change in histology to denote improvement was arbitrary and overestimated virologic response.

Population
Overall, the two clinical trials contained in this NDA provide adequate evidence that a six-month course of treatment with the combination of INTRON A + ribavirin is superior to INTRON A alone in achieving a virologic and histologic response in patients who relapse following a response to previous alfa-interferon therapy.

The results of these studies demonstrate a short-term benefit on three surrogates for response in a selected population of patients with relatively mild and compensated liver disease who had previously responded to interferon monotherapy.. The impact of short-term response on long-term clinical outcomes, such as progression to cirrhosis, liver failure, transplantation, or death remain to be determined. Further investigations into other populations of HCV-infected patients, e.g., patients with more advanced liver disease or patients who have failed previous interferon therapy, should be undertaken.

9.2 Safety

The safety database for this NDA consists of nearly 30,000 patients from controlled studies (n≈2100), or treatment protocols (n≈2,600) and open-label use (n≈25,000).

Deaths were reported patients receiving INTRON A – ribavirin. Cardiovascular-related events in patients with concomitant reductions in hemoglobin levels were reported and accounted for two deaths. Psychiatric related deaths, primarily suicides and illicit drug overdoses in patients with treatment-emergent depression also occurred during treatment with INTRON A + ribavirin. The remaining deaths were generally due to either complications of chronic HCV infection or where unrelated to the disease or treatment.

Adverse events occurred in nearly all of the patients in both relapse studies. The types of events were consistent with those associated with either interferon or ribavirin therapy. The frequency of events was generally higher in the INTRON A + ribavirin arms of the two studies.

It is well established that the interferons cause a spectrum of CNS dysfunctions ranging from mild irritability and memory impairments, to more severe toxicities such as depression and impaired problem solving, psychoses and delerium. A significant proportion of patients reported psychiatric-related adverse events in both treatment arms of the two studies, with insomnia, irritability and depression being the most common. The overall rates of depression reported in the US study were higher than reported in the International study. This difference was most likely accounted for by the general under-reporting of adverse events by non-US investigators. Suicidal behavior, including ideation, attempts and successful suicides, occurred in <1% of all the patients in the safety database. However, it is important to note that patients with significant underlying psychiatric diseases were excluded from study entry. There was no evidence to suggest that ribavirin potentiated the occurrence or severity of these events.

In the two clinical trials reductions in hemoglobin levels was frequently reported in patients treated with INTRON A + ribavirin. Reductions from baseline in hemoglobin levels occurred within 1-2 weeks of the onset of ribavirin therapy. Hemoglobin levels generally stablized by week 4 and returned to normal in most patients within 4-8 weeks after cessation of therapy. Over 10% of patients treated with the combination had a reduction in hemoglobin to less than 10 g/dL compared to no patients in the INTRON A + placebo groups. Certain cardiovascular-related adverse events, including chest pain and dyspnea, occurred more frequently in patients who also had reductions in hemoglobin levels. A higher number of patients who received INTRON A + ribavirin required dose modifications due to anemia. Patients with significant pre-existing cardiovascular disease were excluded from the trials. Therefore, it is not entirely clear how patients with significant underlying cardiovascular disease or decreased cardiac reserve will tolerate this combination. Patients who receive INTRON A + ribavirin should be monitored closely and therapy should be discontinued in patients who exhibit worsening of cardiovascular status.

Thrombocytopenia, neutropenia, and thyroid dysfunction are well-established adverse events associated with INTRON A use, and they occurred at frequencies that were not inconsistent with rates previously reported. Again, there was no apparent increase in either incidence or severity of these events were attributable to ribavirin.

Pregnancies occurred in both female patients and female partners of male patients. INTRON A is a known abortifacient and animal data has demonstrated that ribavirin is teratogenic and embryocidal. Female patients and female partners of male patients who receive treatment with INTRON A + ribavirin will be

exposed to both drugs for an extended period of time. Therefore, there should be widespread education of clinicians and patients about avoiding pregnancy during treatment and for six months following cessation of therapy. Furthermore, there should be careful monitoring of the incidence and outcomes of pregnancies associated with the use of these agents.

10.0 Quality-of-Life

The section of the NDA dealing with Quality-of-Life (QOL) was reviewed by staff in the Division of Drug Marketing, Advertising and Communications. A full report of their findings are included in Appendix C. A summary of the major issues include:

- No information on the development of the specific questions related to QOL in patients with hepatitis was submitted. Without such data, the validity of the instrument could not be substantiated.
- The sponsor failed to pre-specify the QOL endpoints prior to the initiation of the study.
- The sponsor did not specify a minimum meaningful difference for the QOL scales. Therefore, it is unknown if the differences seen were meaningful.

11.0 Labeling

The initial proposed labeling by the applicant was long and provided information mostly drawn from the INTRON A label. Negotiations between the agency and the applicant focused on streamlining the label to provide specific information about INTRON A + ribavirin while retaining important information about the risks of each individual component of the therapy. At a face-to-face meeting between the agency and the applicant on May 5, 1998, general agreement about the format and content of each section of the labeling was reached. The final draft labeling submitted on June 2, 1998, adequately addressed the concerns raised in this NDA review.

Also, during labeling discussions the applicant agreed to develop a Medication Guide for distribution with each dispensed package of Rebetron Combination Therapy. The Medication Guide was requested because the agency was concerned that without risk and adverse event data written in a consumer-friendly manner, patients may not be able to safely use of the products. The draft Medication Guide initially submitted by the applicant required significant revisions; however, it was finalized prior to approval.

12.0 Phase IV Commitments

In the Phase IV (post-marketing) stage of Rebetol/INTRON A development, the applicant has agreed to the following commitments:

- Establish a voluntary pregnancy registry to track the incidence and outcomes of pregnancies that occur in patients or their partners receiving combination therapy. The applicant will provide the agency with periodic reports from the registry.
- Further investigate the impact of food on the safety and efficacy of ribavirin therapy.
- Further investigate whether HCV-RNA and improvements in histology are valid surrogate markers for response to therapy and disease progression.
- Continue to collect long-term follow-up data on patients who participated in company-sponsored trials.
- Design and conduct additional animal carcinogencity studies. The applicant agrees to submit proposals/protocols and obtain FDA concurrence prior to initiation of any studies.

- Investigate the safety and efficacy of the combination in other sub-groups of patients with HCV infection, including naïve, HIV/HCV co-infected, and transplant patients and patients with cirrhotic liver disease.

- Initiate a pediatric development program, and to submit an efficacy supplement with additional pediatric pharmacokinetic and safety data as soon as these data become available.

13.0 Recommended Regulatory Action

Based on the information submitted in NDA 20-903, the application for INTRON A + ribavirin therapy of chronic HCV infection in patients with compensated liver function who have relapsed following alfa-interferon therapy was approved on June 2, 1998.

/s/

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Concurrences:
HFD-530 DivisionDirector/HJolson
HFD-530 ActgTLMO/SKukich SK 6/30/98

CC:
HFD-530 DepDivDir DBirnkrant
HFD-530 NDA 20-903
HFD-530 Division File
HFD-530 Pharm DMorse
HFD-530 Biopharm PRajagopalan
HFD-530 Chemistry RKambhampati
HFD-530 Micro NBattula
HFD-725 GSoon
HFD-344 DSI AEl Hage
HFD-530 CSO TCrescenzi
HFD-530 ClinRev RFleischer
HFD-530 MO TNguyen